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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|-----------------------|---------------------|------------------|
| 09/913,351 | 08/13/2001 | Aurora Brieva Delgado | B-4275PCT 618999-1 | 8629 |

7590 07/21/2003

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[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1653

DATE MAILED: 07/21/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|--------------------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/913,351 | DELGADO ET AL. |
| | Examiner Chih-Min Kam | Art Unit 1653 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 09 May 2003.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

4) Claim(s) 1-10 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-10 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Disposition of Claims

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

 a) All b) Some * c) None of:

 1. Certified copies of the priority documents have been received.

 2. Certified copies of the priority documents have been received in Application No. _____.

 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

 * See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

 a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s) _____.

2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) Other:

DETAILED ACTION

Status of the Claims

1. Claims 1-10 are pending.

Applicants' amendments filed May 9, 2003 (Paper No. 11) is acknowledged, and applicants' response has been fully considered. Claims 1, 3 and 5 have been amended, and new claims 8-10 have been added. Thus, claims 1-10 are examined.

Sequence Listing

2. A copy of Sequence Listing filed May 9, 2003 (Paper No. 11) is acknowledged, and CRF has been entered.

Objection Withdrawn

3. The previous objection to claims 1 and 3 is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 3 in Paper No. 11.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 1-7 under 35 U.S.C.112, second paragraph, regarding the term "and/or", "(LIVM)", is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 3-4 in Paper No. 11.

Informalities

5. The disclosure is objected to because of the following informalities:

The specification cites amino acid sequences at pages 25 and 29, however, no "SEQ ID NO:" is given. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-covalent complex of a polysaccharide and a polypeptide, where the polysaccharide has a defined structure (e.g., MW 150 kDa, one phosphate per 15 monosaccharides, known content of mannose, glucose and galactose), the polypeptide has a minor subunit of SEQ ID NO:2 or 4 and a major subunit of SEQ ID NO:3 or 5 with MW of 11 or 12 kDa, and wherein the molar ratio of the polysaccharide to the polypeptide is about 1: 2.5, does not reasonably provide enablement for a non-covalent glycoconjugate of a polysaccharide and a polypeptide, where the structure of polysaccharide, the sequence of the polypeptide comprising SEQ ID NO:1 (e.g., only 15 out of 230 amino acids are defined) and the molar ratio of the polysaccharide to the polypeptide are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-10 are directed to a non-covalent glycoconjugate of a polysaccharide and a polypeptide, wherein the polysaccharide has a MW of 50-250 kDa, 1 phosphate per 5-25 monosaccharides, 40% mannose and 60% of glucose and galactose, and wherein the polypeptide comprises SEQ ID NO:1, or is a dimer with a minor subunit of SEQ ID NO:2 or 4 and a major

subunit of SEQ ID NO:3 or 5. The specification, however, only discloses cursory conclusions (page 14) without data supporting the findings, which state that the invention describes the formation of non-covalent conjugates of specific polysaccharides and specific polypeptides for manufacturing therapeutic compositions for the treatment of immunological dysfunction, and the conjugates are pharmaceutically active, while none of their components show the pharmaceutical activity of the conjugates. There are no indicia that the present application enables the full scope in view of a non-covalent glycoconjugate of a polysaccharide and a polypeptide as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the polysaccharides and polypeptides in the non-covalent glycoconjugates, and the effects of the glycoconjugates, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed variants in the glycoconjugates except for a non-covalent glycoconjugate of a polysaccharide and a polypeptide, wherein the polysaccharide is isolated from candida utilis cells, and the polypeptide is isolated from Ricinus

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communis seeds having a minor subunit of SEQ ID NO:2 or 4 and a major subunit of SEQ ID NO:3 or 5, and wherein the molar ratio of the polysaccharide and the polypeptide is about 1:2.5 (Examples 1-3) . The specification has not shown the preparation of glycoconjugates containing various polysaccharides and various polypeptides with different molar ratios.

(3). The state of the prior art and relative skill of those in the art:

The specification indicates polysaccharide-protein conjugates with immunomodulatory activities have been described in the prior art, but these conjugates are covalently bonded and come from the same natural source (pages 13-14), while the present invention is directed to non-covalent polysaccharide-protein conjugate. The general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the preparation of non-covalent glycoconjugate using various polysaccharides and polypeptides of SEQ ID NO:1 with different molar ratios and the effects of glycoconjugates to be considered enabling for the claimed variant.

(4). Predictability or unpredictability of the art:

The specification has shown the biological activity of a specific glycoconjugate of a polysaccharide isolated from candida utilis cells and a polypeptide having a minor subunit of SEQ ID NO:2 or 4 and a major subunit of SEQ ID NO:3 or 5 with the molar ratio of the polysaccharide and the polypeptide of 1:2.5 (pages 33-36). However, the specification has not demonstrated the preparation and effects of glycoconjugates containing various polysaccharides and polypeptides of SEQ ID NO:1 with different molar ratios. Because numerous sequences are contained in SEQ ID NO:1 (only 15 out of 230 amino acids are defined), the invention is highly unpredictable regarding the effects of various glycoconjugates in inhibiting the production of TNF.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a non-covalent glycoconjugate of a polysaccharide and a polypeptide, wherein the polysaccharide has a MW of 50-250 kDa, 1 phosphate per 5-25 monosaccharides, 40% mannose and 60% of glucose and galactose, and wherein the polypeptide comprises SEQ ID NO:1. The specification indicates the polysaccharide must comply with certain requirements such as MW in the range of 50-250 kDa, 1 phosphate per 5-25 monosaccharides, having at least 40% mannose, the others being glucose and galactose; the polypeptide must have the consensus sequence of SEQ ID NO:1; and the polysaccharide/polypeptide conjugates can be within 1/1 to 1/19 mol/mol range (pages 14-19). However, the specification has not demonstrated the making and use of the glycoconjugates containing various structures of polysaccharides and various sequences of SEQ ID NO:1 with different molar ratios of the two components. There is no working example indicating the effects of various glycoconjugates except for the glycoconjugate of the polysaccharide isolated from candida utilis cells and the polypeptide having a minor subunit of SEQ ID NO:2 or 4 and a major subunit of SEQ ID NO:3 or 5, with the molar ratio of 1:2.5 (Examples 1-3, pages 33-36). Since the specification fails to provide sufficient teachings on the making of various glycoconjugates, nor demonstrates their biological activities, it is necessary to carry out further experimentation to assess the effects of these various glycoconjugate.

(6). Nature of the Invention

The scope of the claims encompasses a non-covalent glycoconjugate of a polysaccharide and a polypeptide, but the specification does not demonstrate the preparation and the effects of various glycoconjugates. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed variants, the art is unpredictable regarding the effects of claimed glycoconjugates, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of the non-covalent glycoconjugates.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 5 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 8 are indefinite because of the use of the term “to treat disorders of an immunological system related to a higher production of tumor necrosis factor (TNF)”. The term “to treat disorders of an immunological system related to a higher production of tumor necrosis factor (TNF)” renders the claim indefinite, it is unclear what immunological disorders related to higher production of TNF are treated, and what reference point is used for comparison as to “higher production of TNF”.

In response, applicants indicate claim 5 has been amended to specify immunological disorders related to higher production of TNF. The argument is not found persuasive because the

claim does not identify what the immunological disorders are, nor indicates the reference point for "higher production of TNF", thus it is not clear what immunological disorders are treated with the glycoconjugate.

Conclusion

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. *CK*
Patent Examiner

July 19, 2003

Christopher S. F. Low
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